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Applicant:	Maxime Lampilas et al.	Case No.:	8674-000026
Serial No.:	10/727,911	Filing Date:	December 4, 2003
Title:	NOVEL HETEROCYCLIC COMPOUNDS, THEIR PREPARATION AND THEIR USE AS MEDICAMENTS, IN PARTICULAR AS ANTIBACTERIALS AND BETALACTAMASE INHIBITORS		

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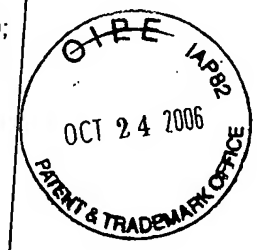

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Due: 10-25-2006	Date Mailed: 10-24-2006	Attorney: MLF/JMW

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.:	10/727,911
Filing Date:	December 4, 2003
Applicant:	Maxime Lampilas et al.
Group Art Unit:	1624
Examiner:	Brenda Libby Coleman
Title:	NOVEL HETEROCYCLIC COMPOUNDS, THEIR PREPARATION AND THEIR USE AS MEDICAMENTS, IN PARTICULAR AS ANTIBACTERIALS AND BETALACTAMASE INHIBITORS
Attorney Docket:	8674-000026

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

AMENDMENT AND PETITION FOR EXTENSION OF TIME

Sir:

In response to the Office Action mailed May 25, 2006, please amend the application as follows and consider the remarks set forth below.

Applicants hereby petition under the provisions of 37 C.F.R. § 1.136(a) for a two-month extension of time in which to respond to the outstanding Office Action and include a fee as set forth in 37 C.F.R. § 1.17(a) with this response for such extension of time.

Amendments to the Claims begin on page 3 of this paper.

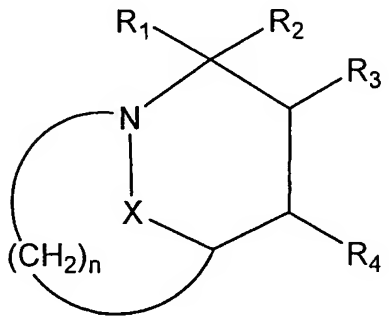
Remarks begin on page 28 of this paper.

AMENDMENTS TO THE CLAIMS

The following listing of claims will replace all prior versions and listings of claims in the application.

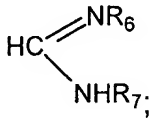
LISTING OF CLAIMS

1. (currently amended) A compound of the ~~general~~ formula:



(I)

in which either:

a) R_1 is a radical selected from the group consisting of hydrogen, COOH, COOR, CN, $(CH_2)_n R_5$, $CONR_6R_7$ and 

;

R is selected from the group consisting of an alkyl radical containing from 1 to 6 carbon atoms, optionally substituted with one or more halogen atoms or with a pyridyl radical; a $-CH_2$-alkenyl radical containing in total from 3 to 9 carbon atoms; a (poly)alkoxyalkyl group containing 1 to 4 oxygen atoms and 3 to 10 carbon atoms; an aryl radical containing from 6 to 10 carbon atoms or an aralkyl radical containing from 7 to 11 carbon atoms, the ~~nucleus of the~~ aryl or aralkyl radical being optionally substituted with a radical selected from the group consisting of OH, NH_2, NO_2, alkyl containing from 1 to

6 carbon atoms, alkoxy containing from 1 to 6 carbon atoms and one or more halogen atoms;

R_5 is selected from the group consisting of COOH, CN, OH, NH_2, $CO\text{-}NR_6R_7$, COOR and OR radicals, R being as defined above,

R_6 and R_7 are individually selected from the group consisting of hydrogen, an alkyl radical containing from 1 to 6 carbon atoms, an alkoxy radical containing from 1 to 6 carbon atoms, an aryl radical containing from 6 to 10 carbon atoms, an aralkyl radical containing from 7 to 11 carbon atoms and an alkyl radical containing from 1 to 6 carbon atoms which is substituted with a pyridyl radical;

n' is equal to 1 or 2,

R_3 and R_4, together with the carbons to which they are attached, form a phenyl or a 5- or 6-membered aromatic heterocycle containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, which is substituted with one or more R' groups, R' being a radical selected from the group consisting of:

$-(O)_a-(CH_2)_b-(O)_a-CONR_6R_7$, $-(O)_a-(CH_2)_b-OSO_3H$, $-(O)_a-(CH_2)_b-SO_3H$,

$-(O)_a-SO_2R$, $-(O)_a-SO_2-CHal_3$, $-(O)_a-(CH_2)_b-NR_6R_7$,

$-(O)_a-(CH_2)_b-NH-COOR$, $-(CH_2)_b-COOH$, $-(CH_2)_b-COOR$, -OR", OH,

$-(CH_2)_b$-phenyl, $-(O)_a-(CH_2)_b-(O)_a-R$, ~~and~~

$-(CH_2)_b$-5- or 6-membered aromatic heterocycle containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, and $-(O)_a-(CH_2)_b$-5- or 6-membered aromatic heterocycle containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, each of said phenyl and said heterocycle being optionally substituted with one or

more substituents selected from halogen, alkyl containing from 1 to 6 carbon atoms, alkoxy containing from 1 to 6 carbon atoms and CF_3,

R, R_6 and R_7 being as defined above,

R" being selected from alkyl radicals containing from 1 to 6 carbon atoms substituted with one or more radicals selected from hydroxy, protected hydroxy, oxo, halogen and cyano radicals,

a being equal to 0 or 1 and b being an integer from 0 to 6,

provided that, when R' is OH, R_1 is $CONR_6R_7$ in which one of R_6 and R_7 is an alkoxy containing from 1 to 6 carbon atoms; or

b) R_4 is hydrogen or $(CH_2)_{n'1}R_5$, wherein n'_1, is 0, 1 or 2 and R_5 is as defined above,

and R_1 and R_3, together with the carbons to which they are attached, form a substituted phenyl or heterocycle, as defined above;

and, in both cases a) and b),

R_2 is selected from the group consisting of hydrogen, halogen, R, $S(O)_mR$, OR, NHCOR, NHCOOR and $NHSO_2R$, R being as defined above and m being 0, 1 or 2,

X is a divalent group -C(O)-B- linked to the nitrogen atom by the carbon atom,

B is a divalent group selected from 1) $-O-(CH_2)_{n"}-$ linked to the carbonyl by the oxygen atom, 2) $-NR_8-(CH_2)_{n"}-$ and 3) $-NR_8-O-$ linked to the carbonyl by the nitrogen atom, n" is 0 or 1 and R_8 is a radical selected from the group consisting of hydrogen, OH, R, OR, Y, OY, Y_1, OY_1, Y_2, OY_2, Y_3, $\underline{O-CH_2-CH_2-S(O-)_m-R}$ ~~$O-CH_2-CH_2-S(O-)m-R$~~, SiRaRbRc and OSiRaRbRc, wherein each of Ra, Rb and Rc is a linear or branched

alkyl containing from 1 to 6 carbon atoms or an aryl containing from 6 to 10 carbon atoms, and R and m are as defined above;

Y is selected from the group consisting of COH, COR, COOR, $CONH_2$, CONHR, CONHOH, $CONHSO_2R$, CH_2COOH, CH_2COOR, CHF-COOH, CHF-COOR, CF_2-COOH, CF_2-COOR, CN, CH_2CN, $CH_2CONHOH$, $CH_2CONHCN$, CH_2tetrazole, protected CH_2tetrazole, CH_2SO3H, CH_2SO_2R, $CH_2PO(OR)_2$, $CH_2PO(OR)(OH)$, $CH_2PO(R)(OH)$ and $CH_2PO(OH)_2$;

Y_1 is selected from the group consisting of SO_2R, SO_2NHCOH, SO_2NHCOR, $SO_2NHCOOR$, $SO_2NHCONHR$, $SO_2NHCONH_2$ and SO_3H;

Y_2 is selected from the group consisting of $PO(OH)_2$, $PO(OR)_2$, PO(OH)(OR) and PO(OH)(R);

Y_3 is selected from the group consisting of tetrazole, tetrazole substituted with R, squarate, NH or NRtetrazole, NH or NRtetrazole substituted with R, $NHSO_2R$, $NRSO_2R$, CH_2tetrazole and CH_2tetrazole substituted with R, R being as defined above,

and n is 1 or 2, or one of its salts with a base or an acid.

2. (original) The compound as claimed in claim 1, wherein n is 1.

3. (original) The compound as claimed in claim 1, wherein R_2 is a hydrogen atom.

4. (original) The compound as claimed in claim 1, wherein R_3 and R_4 together form a substituted phenyl or a substituted heterocycle.

5. (currently amended) The compound as claimed in claim 1 [[4]], wherein R_3 and R_4 together form a substituted phenyl or a substituted heterocycle, wherein the substituted heterocycle is a substituted thienyl or a pyrazolyl substituted with one or more of the substituents therefore as defined in claim 1.

6. (original) The compound as claimed in claim 1, wherein R_1 is selected from the group consisting of hydrogen, $COOCH_3$, $COOC_2H_5$, $CONH_2$, $CONHCH_3$ and $CONHOCH_3$.

7. (original) The compound as claimed in claim 1, wherein B is $-NR_8-(CH_2)_{n''}$ in which n'' is 0.

8. (original) The compound as claimed in claim 1, wherein R_8 is OY in which Y is selected from the group consisting of CH_2COOH, CH_2COOR, CHF-COOH, CHF-COOR, CF_2-COOH, CF_2-COOR, CN, CH_2CN, $CH_2CONHOH$, $CH_2CONHCN$, CH_2tetrazole, protected CH_2tetrazole, CH_2SO_3H, CH_2SO_2R, $CH_2PO(OR)_2$, $CH_2PO(OR)(OH)$, $CH_2PO(R)(OH)$ and $CH_2PO(OH)_2$ and OY1 in which Y_1 is selected from the group consisting of SO_2R, SO_2NHCOR, $SO_2NHCOOR$, $SO_2NHCONHR$ and SO_3H, R being as defined in claim 1.

9. (original) The compound as claimed in claim 1, wherein R' is selected from the group consisting of $-O-CH_2-CHOH-CH_2OH$, $-CH_2-CH_2-NH_2$, $-CH_2-COOC_2H_5$, $-CH_2-CH_2$-phenyl, $-CH_2$-phenyl, -O-CO-NHphenyl, $-O-CO-NHC_2H_5$, $-O-SO_2-CF_3$, -O-

$(CH_2)_2$-O-SO_3H, -O-$(CH_2)_2$-O-CH_3, -CH_2-COOH, -O-CH_2-(2,2-dimethyl-1,3-dioxolan-4-yl), -CO-NH_2, -CO-NH phenyl, -CH_2-(p-OCH_3 phenyl) and phenyl optionally substituted with a substituent selected from CH_3, C_2H_5, F and CF_3.

10. (currently amended) A compound of formula (I), as defined in claim 1, selected from the group consisting of:

- the triethylammonium salt of 5,6-dihydro-6-oxo-N^2-phenyl-5-(sulfoxy)-4*H*-4,7-methanopyrazolo[3,4-e][1,3]diazepine-2,8(8*H*)- dicarboxamide,
- the sodium salt of 4,5,6,8-tetrahydro-6-oxo-5-(sulfoxy)-1*H*-4,7-methanopyrazolo[3,4-e][1,3]diazepine-1-carboxamide,
- the sodium salt of 1,4,5,8-tetrahydro-1-[(4-methoxyphenyl)methyl]-5-(sulfoxy)-6*H*-4,7-methano- pyrazolo[3,4-e][1,3]diazepin-6-one,
- the sodium salt of trans-4,5,6,8-tetrahydro-2-(2-methylphenyl)-6-oxo-5-(sulfoxy)-4,7-methano-7*H*-thieno[2,3-e][1,3]diazepine-8-carboxamide,
- the sodium salt of trans-4,5,6,8-tetrahydro-6-oxo-5-(sulfoxy)-2-[2-(trifluoromethyl)phenyl]-4,7-methano-7*H*-thieno[2,3-e][1,3]diazepine-8-carboxamide,
- the sodium salt of trans-2-(2-ethylphenyl)-4,5,6,8-tetrahydro-6-oxo-5-(sulfoxy)-4,7-methano-7*H*-thieno[2,3-e][1,3]diazepine-8-carboxamide,
- the sodium salt of trans-8-(2,3-dihydroxypropoxy)-1,2,3,5-tetrahydro-3-oxo-2-(sulfoxy)-1,4-methano-4*H*-2,4-benzodiazepine-5-carboxamide,
- the sodium salt of ethyl trans-3-(4-fluorophenyl)-4,6,7,8-tetrahydro-6-oxo-7-(sulfoxy)-5,8-methano-5*H*-thieno[2,3-e][1,3]diazepine-4-carboxylate,

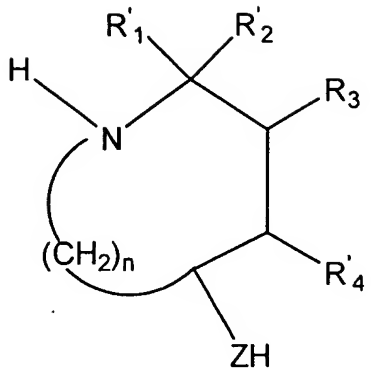
- the sodium salt of trans-2,5,6,8-tetrahydro-6-oxo-2-phenyl-5-(sulfoxy)-4*H*-4,7-methanopyrazolo[3,4-e][1,3]diazepine-8-carboxamide,
- the sodium salt of 1,4,5,8-tetrahydro-1-phenyl-5-(sulfoxy)-6*H*-4,7-methanopyrazolo[3,4-e][1,3]diazepin-6-one,
- the sodium salt of trans-4,5,6,8-tetrahydro-6-oxo-1-pheny-5-(sulfoxy)-1*H*-4,7-methanopyrazolo[3,4-e][1,3] diazepine-8-carboxamide,
- the triethylammonium salt of methyl ~~trans-2,5,6,8-tetrahydro-6-oxo-2-(phenylmethyl)-5-(sulfoxy)-4$_H$-4,7-methanopyrazolo[3,4-e][1,3]-diazepine-8-carboxylate~~ trans-2,5,6,8-tetrahydro-6-oxo-2-(phenylmethyl)-5-(sulfoxy)-4*H*-4,7-methanopyrazolo[3,4-e][1,3] diazepine-8-carboxylate,
- the triethylammonium salt of methyl ~~trans-4,5,6,8-tetrahydro-6-oxo-1-(2-phenylethyl)-5-(sulfoxy)-1$_H$-4,7-methanopyrazolo[3,4-e][1,3]~~ trans-4,5,6,8-tetrahydro-6-oxo-1-(2-phenylethyl)-5-(sulfoxy)-1*H*-4,7-methanopyrazolo[3,4-e][1,3] diazepine-8-carboxylate,
- the triethylammonium salt of ethyl trans-4,5,6,8-tetrahydro-8-(methoxycarbonyl)-6-oxo-5-(sulfoxy)-1*H*-4,7-methanopyrazolo [3,4-e][1,3] diazepine-1-acetate,
- the triethylammonium salt of ethyl trans-5,6-dihydro-8-(methoxycarbonyl)-6-oxo-5-(sulfoxy)-4*H*-4,7-methanopyrazolo [3,4-e][1,3]diazepine-2(8H)-acetate,
- the di(triethylammonium) salt of trans-5,6-dihydro-8-(methoxycarbonyl)-6-oxo-5-sulfoxy-4*H*-4,7-methanopyrazolo [3,4-e][1,3]diazepine-2(8*H*)acetic acid,

- the pyridinium salt of methyl trans-1-(aminocarbonyl)-4,5,6,8-tetrahydro-6-oxo-5-(sulfoxy)-1*H*-4,7-methanopyrazolo[3,4-e][1,3]diazepine-8-carboxylate,
- the pyridinium salt of methyl ~~trans-2-(aminocarbonyl)-2,5,6,8-tetrahydro-6-oxo-5-(sulfoxy)-4*H*-4, 7-methanopyrazolo[3,4-e]diazepine-8-carboxylate~~ trans-2-(aminocarbonyl)-2,5,6,8-tetrahydro-6-oxo-5-(sulfoxy)-4*H*-4, 7-methanopyrazolo[3,4-e][1,3]diazepine-8-carboxylate,
- the sodium salt of methyl trans-2-(4-fluorophenyl)-4,5,6,8-tetrahydro-6-oxo-5-(sulfoxy)-4,7-methano-7*H*-thieno[2,3-e][1,3]diazepine-8-carboxylate,
- the sodium salt of methyl trans-2(aminocarbonyl)-4,5,6,8-tetrahydro-6-oxo-5-(sulfoxy)-4,7-methano-7-*H*-thieno[2,3-e][1,3]diazepine-8-carboxylate,
- the sodium salt of ethyl trans-1,2,3,5-tetrahydro-3-oxo-9-[[(phenylamino)carbonyl]oxy]-2-(sulfoxy)-1,4-methano-4*H*-2,4-benzodiazepine-5-carboxylate,
- the sodium salt of trans-1,2,3,5-tetrahydro-N-methoxy-8-[(2-methoxyethoxy)methoxy]-3-oxo-2-(sulfoxy)-1,4-methano-4*H*-2,4-benzodiazepine-5-carboxamide,
- the sodium salt of ethyl trans-1,2,3,5-tetrahydro-3-oxo-8-[[(phenylamino)carbonyl]oxy]-2-(sulfoxy)-1,4-methano-4*H*-2,4-benzodiazepine-5-carboxylate,

- the sodium salt of ethyl trans-8-[[(ethylamino)carbonyl]oxy]-1,2,3,5-tetrahydro-3-oxo-2-(sulfoxy)-1,4-methano-4*H*-2,4-benzodiazepine-5-carboxylate,
- the sodium salt of ethyl ~~trans-1,2,3,5-tetrahydro-3-oxo-2-(sulfoxy)-8-[[trifluoromethyl)sulfonyl]oxy]-1,4-methano-4*H*-2,4-benzodiazepine-5-carboxylate~~ trans-1,2,3,5-tetrahydro-3-oxo-2-(sulfoxy)-8-[[(trifluoromethyl)sulfonyl]oxy]-1,4-methano-4*H*-2,4-benzodiazepine-5-carboxylate,
- the disodium salt of trans-1,2,3,5-tetrahydro-3-oxo-2-(sulfoxy)-8-[2-(sulfoxy)ethoxy]-1,4-methano-4*H*-2,4-benzodiazepine-5-carboxamide,
- the sodium salt of trans-8-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]-1,2,3,5-tetrahydro-3-oxo-2-(sulfoxy)-1,4-methano-4*H*-2,4-benzodiazepine-5-carboxamide, and
- the triethylammonium salt of methyl trans-2,5,6,8-tetrahydro-6-oxo-(2-phenylethyl)-5-(sulfoxy)-4*H*-4,7-methanopyrazolo[3,4-e][1,3]diazepine-8-carboxylate.

11. (currently amended) A method for preparing a compound as claimed in claim 1, which comprises:

a) reacting a carbonylating agent, where appropriate in the presence of a base, with a compound of formula (II):



(II)

in which either:

a) R'_1 is selected from the group consisting of H, CN, protected COOH, $COOR_9$, $(CH_2)_{n'}R'_5$, $CONR_6R_7$ and

R_9 is selected from the group consisting of alkyl containing from 1 to 6 carbon atoms, optionally substituted with one or more halogen atoms or with a pyridyl; $-CH_2-$alkenyl containing in total from 3 to 9 carbon atoms; aryl containing from 6 to 10 carbon atoms or aralkyl containing from 7 to 11 carbon atoms, the nucleus of the aryl or aralkyl being optionally substituted with a substituent selected from the group consisting of NO_2, protected OH, protected NH_2, alkyl containing from 1 to 6 carbon atoms, alkoxy containing from 1 to 6 carbon atoms and one or more halogen atoms;

R'_5 is selected from the group consisting of protected OH, CN, protected NH_2, $CO\text{-}NR_6R_7$, protected COOH, $COOR_9$, and OR_9, R_9 being as defined above; n', R_6 and R_7 are as defined in claim 1;

R_3 and R'_4, together with the carbons to which they are attached, form a phenyl or a 5- or 6-membered aromatic heterocycle containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, and optionally substituted with one or more R_{10} groups, R_{10} being selected from the group consisting of hydrogen; alkyl containing

from 1 to 6 carbon atoms substituted with one or more substituents selected from hydroxy, oxo, halogen and cyano; alkenyl containing from 2 to 6 carbon atoms; halo; protected OH; -OR; and OR"; wherein R" is as defined in Claim 1, ~~R" being as defined above~~; $-(CH_2)_b$-phenyl and $-(CH_2)_b$-heterocycle, each of said phenyl and heterocycle being optionally substituted, as defined in claim 1; or

b) R'_4 represents a hydrogen atom or $(CH_2)_n$'1 R'_5, n'_1 being 0, 1 or 2 and R'_5 being as defined above,

and R'_1 and R_3 together form an optionally substituted phenyl or heterocycle as defined above for R_3 and R'_4;

and, in both cases a) and b),

R'_2 is selected from the group consisting of hydrogen, halogen, R_9, $S(O)_mR_9$, OR_9, NHCOH, $NHCOR_9$, $NHCOOR_9$ and $NHSO_2R_9$, R_9 being as defined above and m being as defined in claim 1,

n being as defined in claim 1;

ZH is selected from the group consisting of $HO-(CH_2)_{n"}$, $HNR'_8-(CH_2)_{n"}$- and HNR'_8-O-, n" being as defined in claim 1 and R'_8 being selected from the group consisting of hydrogen, R_9, protected OH, OR_9, Y', OY', Y'_1, OY'_1, Y'_2, OY'_2, Y'_3, $O-CH_2-CH_2-S(O)_m$-R", SiRaRbRc and OSiRaRbRc, each of Ra, Rb and Rc individually being a linear or branched alkyl containing from 1 to 6 carbon atoms or an aryl containing from 6 to 10 carbon atoms, R_9 and m being as defined above,

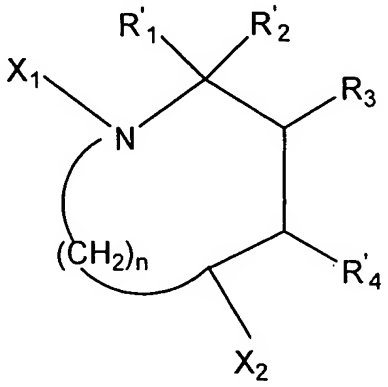
Y' is selected from the group consisting of COH, COR_9, $COOR_9$, $CONH_2$, $CONHR_9$, $CONHSO_2R_9$, CH_2COOR_9, protected CH_2tetrazole, $CH_2SO_2R_9$, $CH_2PO(OR_9)_2$, protected CONHOH, protected CH_2COOH, protected $CH_2CONHOH$,

protected CH_2SO_3, protected $CH_2PO(OR)(OH)$, protected $CH_2PO(R)(OH)$ and protected $CH_2PO(OH)_2$,

Y'_1 is selected from the group consisting of SO_2R_9, SO_2NHCOH, SO_2NHCOR_9, $SO_2NHCOOR_9$, $SO_2NHCONH_2$, $SO_2NHCONHR_9$ and protected SO_3H,

Y'_2 is selected from the group consisting of $PO(OR_9)_2$, protected $PO(OH)_2$, protected $PO(OH)(OR)$ and protected $PO(OH)(R)$,

Y'_3 is selected from the group consisting of protected tetrazole, tetrazole substituted with R_9, protected squarate, protected NHtetrazole, protected NR_9tetrazole, protected NH, NR_9tetrazole substituted with R_9, $NHSO_2R_9$ and NSO_2R_9, R_9 being as defined above, and n is as defined in claim 1; in order to obtain an intermediate compound of formula (III):



(III)

in which: R'_1, R'_2, R_3, R'_4 and n have the same meanings as above and either X_1 is hydrogen and X_2 is -Z-CO-X_3, X_3 representing the residue of the carbonylating agent, or X_2 is -ZH and X_1 is CO-X_3, X_3 being as defined above; and

b) cyclizing said intermediate in the presence of a base; and

c) where appropriate, step a) is preceded and/or step b) is followed by one or more of the following reactions, in an appropriate order:

- protection of the reactive functional groups;
- deprotection of the reactive functional groups;
- esterification;
- saponification;
- sulfation;
- phosphatization;
- amidation;
- acylation;
- sulfonylation;
- alkylation;
- formation of a urea group;
- reduction of carboxylic acids;
- reduction of ketones and aldehydes to alcohols;
- salification;
- ion exchange;
- resolution or separation of diastereoisomers;
- oxidation of sulfide to sulfoxide and/or sulfone;
- oxidation of aldehyde to acid;
- oxidation of alcohol to ketone;
- halogenation or dehalogenation;
- carbamoylation;

- carboxylation;
- introduction of an azido group;
- reduction of an azido to amine;
- reactions of coupling of aromatic or heteroaromatic halides or triflates or of heterocyclic nitrogens with aryl- or heteroarylboronic acids;
- reactions of coupling of aromatic or heteroaromatic halides or triflates with stannyl-containing reagents; hydrogenation of double bonds;
- dihydroxylation of double bonds;
- cyanidation.

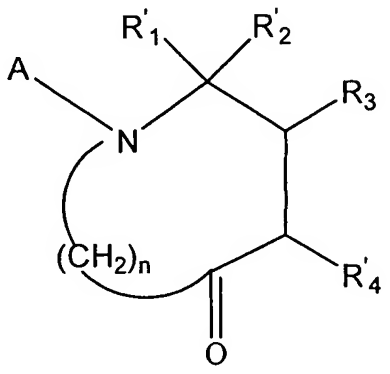
12. (original) The method as claimed in claim 11, wherein the carbonylating agent is selected from the group consisting of phosgene, diphosgene, triphosgene, aryl, aralkyl, alkyl and alkenyl chloroformates, alkyl dicarbonates, carbonyldiimidazole and mixtures thereof.

13. (original) The method as claimed in claim 11, wherein the carbonylation reaction occurs in the presence of a base.

14. (original) The method as claimed in claim 11, wherein, in step b), the base is selected from the group consisting of amines, hydrides, alcoholates, amides and carbonates of alkali or alkaline earth metals.

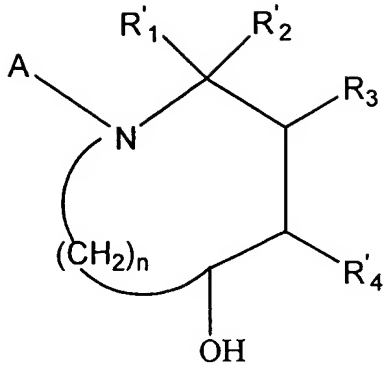
15. (original) The method as claimed in claim 14, wherein the base is an amine.

16. (currently amended) The method as claimed in claim 11, wherein the compound of formula (II) in which ZH is selected from $HO-(CH_2)_{n''}-$, $HNR'_8-(CH_2)_{n''}-$ in which n'' is 0, and HNR'_8-O-, R'_8 being as defined in claim 11, is obtained by a method wherein a compound of formula (IV):



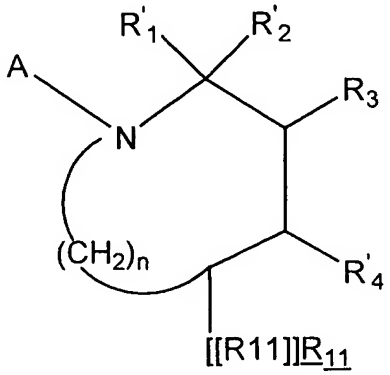
(IV)

in which R'_1, R'_2 and n are as defined in claim 11, R_3 and R'_4 have the values defined in claim 11 or else values which are precursors of the values defined above and A represents hydrogen or a group protecting the nitrogen, is treated with a reducing agent, in order to obtain a compound of formula (V):



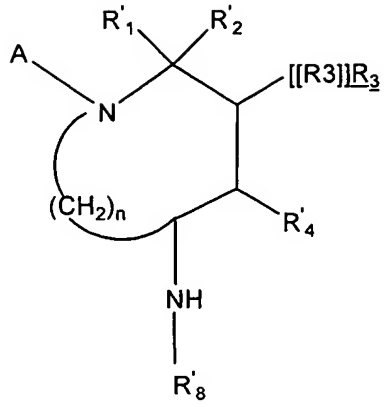
(V)

in which A is as defined above and[[,]] R'$_1$, R'$_2$, R$_3$, R'$_4$ and n are as defined in claim 11, and in which, where appropriate, the OH group is replaced with a leaving group, in order to obtain a compound of formula (VI):

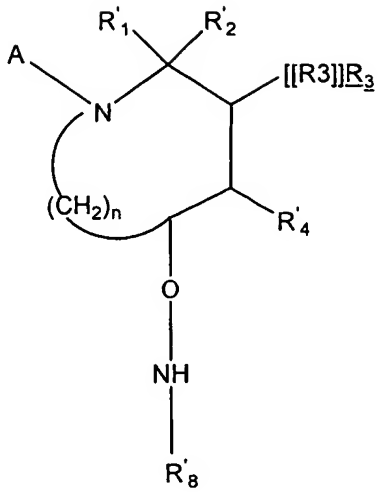


(VI)

in which A is as defined above and[[,]] R'$_1$, R'$_2$, R$_3$, R'$_4$ and n are as defined in claim 11 and R_{11} represents a leaving group, which compound (VI) is then treated with a compound of formula Z_1H_2 in which Z_1 is a divalent group -NR'$_8$ or -O-NR'$_8$, R'$_8$ being as defined in claim 11, in order to obtain a compound of formula (VIII) or (VIII'):



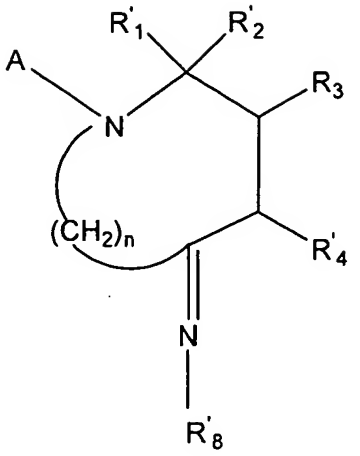
(VIII)



(VIII')

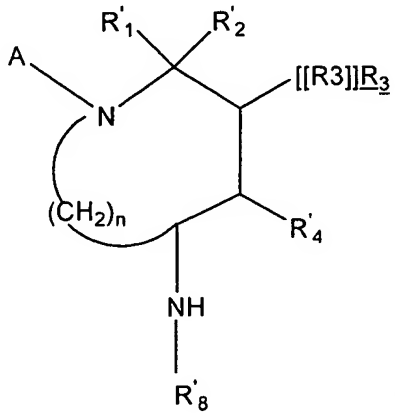
in which A is as defined above and[[,]] R'_1, R'_2, R_3, R'_4, n ~~n"~~ and R'_8 are as defined in claim 11, and then, where appropriate, with an appropriate agent for deprotecting the nitrogen atom, and wherein, where appropriate, the intermediate of formula (IV), (V), (VIII) or (VIII') is subjected to one or more of the reactions described in step c) of the method of claim 11, in an appropriate order.

17. (currently amended)The method as claimed in claim 11, wherein the compound of formula (II) in which ZH is NHR'_8-$(CH_2)_{n"}$- in which n" is 0 is obtained by a method in which a compound of formula (IV) as defined above is treated with a compound of formula $H_2NR'_8$, in order to obtain a compound of formula (VII):



(VII)

in which A represents hydrogen or a group protecting the nitrogen and wherein R'_1, R'_2, R_3, R'_4, n and R'_8 are as defined in claim 11, which compound of formula (VII) is reacted with a reducing agent in order to obtain a compound of formula (VIII):



(VIII)

in which A is as defined above, R'_1, R'_2, R_3, R'_4, n ~~n'~~ and R'_8 are as defined in claim 11, which compound of formula (VIII) is treated, where appropriate, with an appropriate agent for deprotecting the nitrogen atom, and wherein, where appropriate, the intermediate of formula (VII) or (VIII) is subjected to one or more of the reactions described in step c) of the method of claim 11, in an appropriate order.

18. (original) A method of treating a bacterial infection comprising administering to a mammal in need thereof an antibacterially effective amount of a compound as defined in claim 1, or a salt thereof with a pharmaceutically acceptable acid or base.

19. (original) A method of treating a bacterial infection comprising administering to a mammal in need thereof an antibacterially effective amount of a compound as defined in claim 10, or a salt thereof with a pharmaceutically acceptable acid or base.

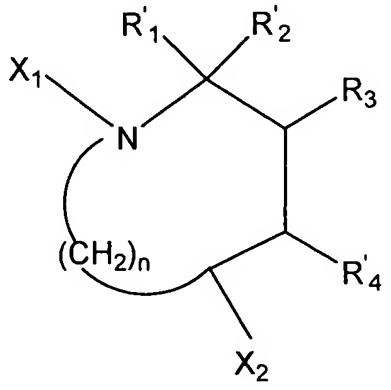
20. (original) A pharmaceutical composition containing, as an active ingredient, at least one compound as claimed in claim 1.

21. (original) A pharmaceutical composition containing, as an active ingredient, at least one compound as claimed in claim 10.

22. (currently amended) A pharmaceutical composition containing~~, as~~ an active ingredient comprising [[,]] at least one β-lactamase inhibiting agent comprising a compound as defined in ~~medicament as defined in~~ claim 1 ~~and at least one β-lactam agent medicament~~.

23. (currently amended) A pharmaceutical composition containing~~, as~~ an active ingredient [[,]] at least one β-lactamase inhibiting agent ~~medicament~~ comprising a compound as defined in claim 10 ~~and at least one β-lactam medicament~~.

24. (withdrawn) A compound of general formula (III) or one of its salts with an acid:

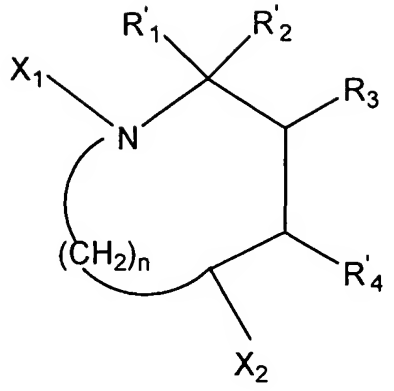


(III)

in which R_3 and R'_4 or R'_1 and R_3 together with the carbon atoms to which they are attached, form a phenyl or an aromatic heterocycle, which is substituted with $-(CH_2)_b-$ phenyl or $-(CH_2)_b-$ aromatic heterocycle, which is optionally substituted, as defined in claim 11.

25. (withdrawn) A compound of claim 24 wherein said salt is a hydrochloride or trifluoroacetate.

26. (withdrawn) A compound of general formula (III) or one of its salts with an acid:

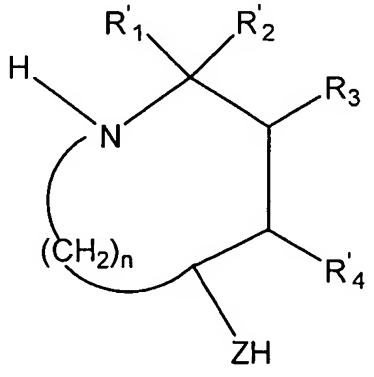


(III)

in which R'_1 is $CONR_6R_7$ in which R_6 or R_7 is an alkoxy radical containing from 1 to 6 carbon atoms, all the other values being as defined in claim 11.

27. (withdrawn) A compound of claim 26 wherein said salt is a hydrochloride or trifluoroacetate.

28. (withdrawn) A compound of formula (II) or one of its salts with an acid:

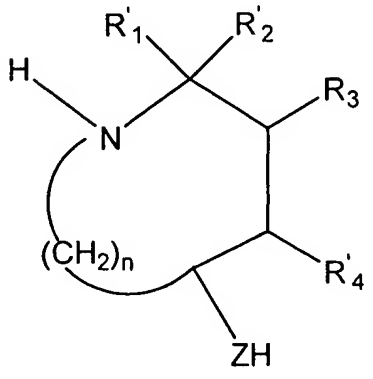


(II)

in which R_3 and R'_4 or R'_1, and R_3, together with the carbons to which they are attached, form a phenyl or an aromatic heterocycle, which is substituted with $-(CH_2)_b$-phenyl or $-(CH_2)_b$-aromatic heterocycle, which is optionally substituted, as defined in claim 11.

29. (withdrawn) A compound of claim 28 wherein said salt is a hydrochloride or trifluoroacetate.

30. (withdrawn) A compound of formula (II) or one of its salts with an acid:

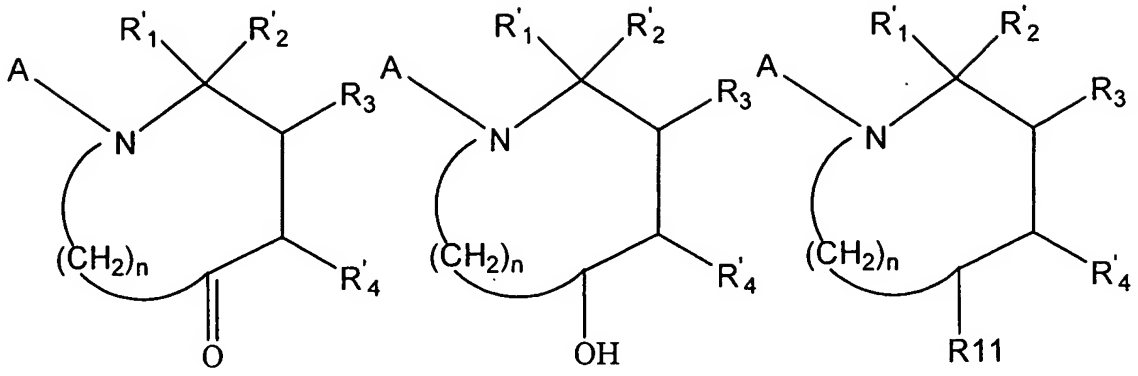


(II)

in which R'_1 is $CONR_6R_7$ in which R_6 or R_7 is an alkoxy radical containing from 1 to 6 carbon atoms, all the other values being as defined in claim 11.

31. (withdrawn) A compound of claim 30 wherein said salt is a hydrochloride or trifluoroacetate.

32. (withdrawn) A compound of formulae (IV), (V) or (VI) or one of its salts with an acid:



(IV) (V) (VI)

in which A and R_{11} are as defined in claim 16 and all the other values are as defined in claim 11.

33. (withdrawn) A compound of claim 32 wherein said salt is a hydrochloride or trifluoroacetate.

34. (withdrawn) A compound selected from the compounds of formulae (IV), (V) and (VI) or one of its salts with an acid, in which R'_1 is as defined in claim 11 and all the other values are as defined in claim 16.

35. (withdrawn) A compound of claim 34 wherein said salt is a hydrochloride or trifluoroacetate.

36. (withdrawn) A compound selected from the compounds of formulae (VII),

(VIII) and (VIII') or one of its salts with an acid: 32in which A and R'_8 are as defined in claim 17 and all the other values are as defined in claim 11.

37. (withdrawn) A compound of claim 36 wherein said salt is a hydrochloride or trifluoroacetate.

38. (withdrawn) The compound of formulae (VII) and (VIII) or one of its salts with an acid, in which R'_1 is as defined in claim 11 and all the other values are as defined in claim 17.

39. (withdrawn) A compound of claim 38 wherein said salt is a hydrochloride or trifluoroacetate.

40. (currently amended) A method of treating a bacterial infection comprising administering to a mammal in need thereof an ~~a β- bata-lactamase inhibiting~~ effective amount of a β-lactamase inhibiting agent comprising a compound as defined in claim 1, or a salt thereof with a pharmaceutically acceptable acid or base and ~~together with~~ an antibacterially effective amount of a beta-lactam medicament agent.

41. (currently amended) A method of treating a bacterial infection comprising administering to a mammal in need thereof an ~~a β- bata-lactamase inhibiting~~ effective amount of a β-lactamase inhibiting agent comprising a compound as defined in claim

REMARKS

Claims 1-41 are now pending in the application. Claims 24-39 have been withdrawn from consideration. Claims 1, 5, 10-11, 16-17, 22-23, and 40-41 have been amended to address mere informalities. The amendments to the claims contained herein are intended to be of equivalent scope as originally filed and, thus, are not narrowing amendments. The Examiner is respectfully requested to reconsider and withdraw the rejections in view of the amendments and remarks contained herein.

REJECTION UNDER 35 U.S.C. § 112

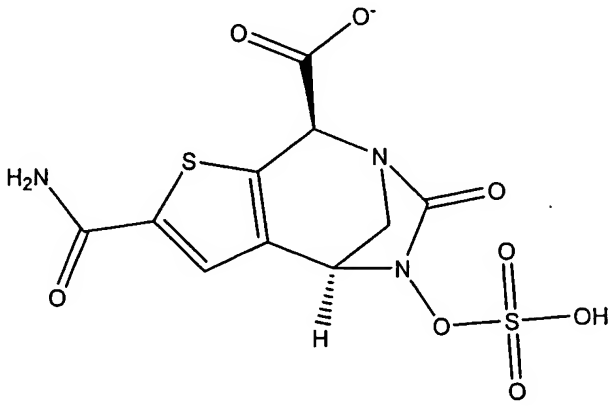
Claims 1-23, 40 and 41 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point and distinctly claim the subject matter which Applicants regard as the invention. This rejection is respectfully traversed. As described above, Claims 1, 10-11, 16-17, 22-23, and 40-41 have been amended and Applicants respectfully submit that the claims are in condition for allowance.

Claim 1 has been amended to delete "general" in the preamble (Paragraph (a)); to delete "nucleus of the" aryl or aralkyl radical (Paragraph (b)); to recite $O\text{-}CH_2\text{-}CH_2\text{-}S(O\text{-})_m\text{-}R$, where m applies to the $(O\text{-})_m$ repeating group in R_8 (Paragraph (c)); and to add R' species $\text{-}(O)_a\text{-}(CH_2)_b\text{-}(O)_a\text{-}R$, and $\text{-}(O)_a\text{-}(CH_2)_b$-5- or 6-membered aromatic heterocycle containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, such that Claim 9 has sufficient antecedent basis (Paragraph (d)).

Claim 10 has been amended to modify 4H and 1H (Paragraphs (e) and (f)). Further, Claim 10 has been amended to recite the triethylammonium salt of methyl

trans-2,5,6,8-tetrahydro-6-oxo-2-(phenylmethyl)-5-(sulfoxy)-4*H*-4,7-methanopyrazolo [3,4-e][1,3] diazepine-8-carboxylate to indicate the position of the nitrogen atoms in diazepine (Paragraph (g)).

With regard to the rejection of Claim 10 under Paragraph (h), Applicants believe that the nomenclature of the tenth species is clear to those of skill in the art, in that the 2(aminocarbonyl) group is at the 2-position of the thienyl ring. The structure of the tenth species is:



trans-2(aminocarbonyl)-4,5,6,8-tetrahydro-6-oxo-5-(sulfoxy)-4,7-methano-7-H-thieno[2,3-e][1,3]diazepine-8-carboxylate

Thus, Applicants traverse the rejection set forth in Paragraph (h), as the nomenclature set forth in Claim 10 is definite.

With regard to the rejection of Claim 10 under Paragraph (i), the amendment to Claim 1 described above regarding additional R′ species provides sufficient antecedent basis for the twelfth species.

Claim 10 has also been amended to recite the sodium salt of ethyl trans-1,2,3,5-tetrahydro-3-oxo-2-(sulfoxy)-8-[[(trifluoromethyl)sulfonyl]oxy]-1,4-methano-4*H*-2,4-benzodiazepine-5-carboxylate. Paragraph (j).

Claim 11 has been amended to clarify that R″ is as defined in Claim 1 to address the Paragraph (k) rejection of Claims 11 – 17. Claim 11 has likewise been amended to

10, or a salt thereof with a pharmaceutically acceptable acid or base and ~~together with~~ an antibacterially effective amount of a beta-lactam medicament agent.

include a reference to n as defined in Claim 1, to obviate the rejection of Claim 16 (Paragraph (l)). Claim 16 has been amended in several locations to recite that A is as defined in Claim 16 and n is as defined in Claim 11 (Paragraphs (m-n)). Formula VI has been amended to include R_{11}, Formula VIII and VIII' have been amended to recite R_3. Paragraphs (o-r).

Claim 17 has been amended to recite that A represents hydrogen or a group protecting nitrogen to address Paragraph (s). Further, n is as defined in Claim 11 and in the formulas set forth in Claim 17. Similarly, Formula VIII has been amended to recite R_3. Paragraphs (s-u).

Claims 22, 23 have been amended to clarify the claimed invention, which now recites a pharmaceutical composition that contains an active ingredient comprising at least one β-lactamase inhibiting agent comprising a compound as defined in Claims 1 and 10, respectively. Similarly, Claims 40 and 41 have been amended to more particularly point out and distinctly claim a method of treating a bacterial infection comprising administering to a mammal in need thereof an effective amount of a β-lactamase inhibiting agent comprising a compound as defined in Claims 1 and 10, respectively. The method also comprises administering an antibacterially effective amount of a beta-lactam medicament agent. Support for these amendments is found throughout the specification as originally filed and at Page 23 line 18 bridging Page 24 line 2. Applicants submit that these amendment overcome the rejection set forth at Paragraph (v). Applicants respectfully submit that the amendments made to Claims 1, 10-11, 16-17, 22-23, and 40-41 overcome the indefiniteness rejections and are presently in condition for allowance.

REJECTION UNDER DOUBLE PATENTING

Applicants note that Claims 1-10, 20 and 21 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-10 and 20 of co-pending U.S. Application Serial No. 10/480,019. Applicants reserve the right to respond to this rejection at the appropriate time, if the rejection should become non-provisional.

CLAIM REJECTIONS – 37 CFR 1.75(C)

Claim 5 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must be stated in the alternative. This rejection is respectfully traversed.

Claim 5 has been amended to depend solely from Claim 1. In this regard, Applicants respectfully submit that the amendment overcomes the objection and that Claim 5 is presently in condition for allowance.

CONCLUSION

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the outstanding Office Action and the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested. If the Examiner

believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

Dated: October 24, 2006

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